IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Gleave, et al.	
Application No.: 10/646,436	
Filed: 8/21/2003	Group Art Unit: 1635
Title: RNAi Probes Targeting Cancer-Related Proteins	Examiner: Kimberly Chong
Attorney Docket No.: UBC.P-030	

BRIEF FOR APPELLANT

This brief is filed in support of Applicants' Appeal from the final rejection mailed 2/19/2010. Consideration of the application and reversal of the rejections are respectfully urged.

Real Party in Interest

The real party in interest is The University of British Columbia. The invention is licensed to OncoGenex Technologies Inc. which is a 100% subsidiary of OncoGenex Pharmaceuticals, Inc.

Related Appeals and Interferences

The appeal is the second appeal of this application. The previous appeal was decided April 22, 2008, and a copy of the decision in that appeal is attached in the Appendix hereto.

Status of Claims

Claims 1, 4, 10, 11, 14, 35 and 36 are pending and are the subject of this appeal. Claims 20, 23, 29 and 37 are withdrawn from consideration but would be recombined if the pending claims are found to be allowable. Claims 2, 3, 5-9, 12, 13, 15-19, 21, 22, 24-28, and 30-34 have been canceled.

Status of Amendments

No amendment after final was filed.

Summary of Claimed Subject Matter

The present invention relates to an RNA molecule that comprises or consists of a sequence of bases as defined by Seq. ID No. 10 (Page 7, Table 1), and to a pharmaceutical composition that contains this RNA molecule (original claims 10 and 11). The RNA molecule may be double stranded with one of the strands consisting of Seq ID No. 10 (claims 35 and 36).

The RNA molecule of the invention mediates degradation or blocks translation of mRNA that is the transcriptional product of a target gene, wherein the target gene encodes clusterin. (Page 23-27; Examples 7-20)

Grounds of Rejection to be reviewed on Appeal

1. Claims 1, 4, 10, 11, 14, 35 and 36 stand rejected under 35 USC § 103 as obvious over the combination of Miyake et al, Tuschl et al, and Holen et al.

2. Claims 1, 4, 10, 11, 14, 35 and 36 stand rejected under 35 USC § 103 as obvious over the combination of Miyake et al, Tuschl et al, Fosnaugh et al, and Hammond et al.

Argument

I. Preliminary Statement

The claims of this application relate to RNA molecules that comprise or consist of Seq ID No. 10, or a double stranded RNA in which one of the strands consists of Seq ID No: 10. Seq ID No: 10 has the sequence "gcagcagagu cuucaucaut t," in which the terminal "tt" is included as part of the structure for activity as an siRNA. This sequence overlaps with and targets the translation initiation site of the clusterin gene. The claims of this application are thus substantially narrower than the claims that were at issue in the earlier appeal of this application.

II. The Teachings of the References

In any evaluation of obviousness, a first step in the analysis should be a determination of the scope and content of the prior art. In this case, the claims are rejected as obvious over either of two sets of references, in which the first two references are the same.

Miyake et al. teaches a DNA antisense oligodeoxynucleotide that targets clusterin. The sequence of this oligodeoxynucleotide, as set forth in Miyake is: cagcagcagagtcttcatcat. This is not identical to presently claimed Seq ID No. 10 (although the target site, i.e. the part of the clusterin gene with which there is sequence specificity, is generally the same). Indeed, the alignment of the two sequences is

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  g cagcagaguc uucaucautt
cag cagcagagtc ttcatcat
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Hammond, Tuschl, Fosnaugh and Holen relate to a technique of gene silencing known as RNA interference that uses RNA sequences (siRNA) to control the expression of a gene. These references have nothing to do with clusterin, and do not teach any specific sequence that is similar to Seq ID No. 10.

The mechanism of action of antisense molecules and siRNA molecules is understood to be quite different. As outlined in Hammond, Figure 1, the activity of siRNA involves the formation of a RISC which in turn causes enzymatic destruction of mRNAs recognized by the siRNA guide within the RISC.

Tuschl also describes the mechanism of siRNA action, and makes extensive reference to target-specific RNA interference, the reference does not contain any particular guidelines on the selection of target sites within a target gene sequences. It is to be noted, however, that the sequences tested in Figure 1 start at 93 or more bases after the start codon, which clearly does not suggest the selection of Seq. ID No. 10 for clusterin.

Fosnaugh does, as stated by the examiner, provide in example 3, a protocol for selecting siRNA target sites. The Examiner has not, however, shown that applying the methodology of Fosnaugh would result in the selection of Seq. ID No. 10.

Holen teaches that "sites in mRNA targets are differentially accessible to ribozymes and oligodeoxynucleotides" (p. 1757, Col. 2) and tested whether position effects were important for siRNA. The reference selected siRNA based on ribozyme accessibility (p. 1758, Col. 2), not antisense accessibility. Furthermore, Holen discloses that siRNA targeting the translation initiation site was "essentially inactive." (*Id.*)

III. Differences Between the Art and Claimed Invention

The key difference between the cited art and the claimed invention is that the sequence that is similar to the presently claimed Seq ID No. 10 is a DNA sequence and the claimed sequence is an RNA sequence.

IV. There is No *Prima Facie* Case of Obviousness Presented over the Combination of Miyake et al, Tuschl et al, and Holen et al. (Ground of Rejection 1)

The Examiner's rationale appears to be that there is a reason in the art for reducing the expression of clusterin, and a known DNA antisense sequence for this purpose. There is also another technique known for gene silencing that makes use of RNA instead of DNA. Therefore, in the Examiner's view, it would have been obvious to make an RNA counterpart of the known DNA molecule. This argument is beguiling in its simplicity, but it fails because there is no argument or evidence of record that such a simple change can be made with any expectation of success.

As all of the cited references relating to RNA interference teach, the mechanism of action of the RNA molecules, which are active in the form of double-stranded RNA, is entirely different from the mechanism of action of DNA antisense. The Examiner has produced neither evidence

nor reasoned argument that a person skilled in the art would ignore this difference in mechanism to predict that an RNA counterpart of a DNA antisense would have activity.

The references further teach steps to arrive at predictions of useful sequences for use in RNA interference. The Examiner has not shown that application of these steps to the clusterin target would lead a person skilled in the art to the particular sequence now being claimed. Furthermore, reasoned analysis indicates that such a showing could not be made.

Tuschl teaches a variety of sequences that were tested for use in inhibiting a non-clusterin target. These sequences are shown in Figure 1 of Tuschl and start at 93 or more bases after the start codon. Thus, nothing in Tuschl suggests the region adjacent the start codon (the location targeted by Seq. ID No. 10) as a desirable location.

Holen teaches that "sites in mRNA targets are differentially accessible to ribozymes and oligodeoxynucleotides" (p. 1757, Col. 2) and tested whether position effects were important for siRNA. The reference selected siRNA based on ribozyme accessibility (p. 1758, Col. 2), not antisense accessibility. Thus, the reference does not teach that DNA antisense sequences are valid starting points for identifying sequences for RNA interference and by its silence on this point it arguably teaches away from such a choice.

Furthermore, Holen discloses that siRNA targeting the translation initiation site was "essentially inactive." (*Id.*) Thus, this reference also teaches away from an expectation that the selection of a sequence at this location for RNA interference will be successful.

Thus, the cited references provide no basis for a *prima facie* case of obviousness relative to the presently claimed invention which is directed to one specific sequence, or to a double stranded species containing this sequence as one strand as presently claimed.

V. <u>There is No Prima Facie Case of Obviousness Presented over the Combination of Miyake et al, Tuschl et al, Fosnaugh et al, and Hammond et al. (Ground of Rejection 2)</u>

Miyake et al and Tuschl are discussed above. Hammond teaches the mechanism for RNA interference and shows that it is different from DNA based antisense.

Fosnaugh teaches in example 3 a protocol for selecting siRNA target sites. In this regard, it is noted that Seq ID No. 10, does not meet the requirements of step 7 (¶ 240) of Fosnaugh. The Examiner asserts that this requirement is met (Final Office Action, Page 4) because this step requires ranking targets for overhang regions and Seq ID No. 10 has overhang regions. The reference however, requires ranking the pieces of the **target** for overhang regions (i.e. places where there is an "aa" or a "tt" in the target sequence. In the clusterin sequence, the last two bases if one based them on the actual target sequence **would not be tt.** Rather they would be "gc" based on the known sequence of the clusterin gene. Accordingly, as Applicants have argued, the target sequence corresponding to Seq ID No. 10 would not be one selected using the rules of Fosnaugh.

Furthermore, it should be noted that the Miyake's sequence does in fact contain a "tt". Thus, following Fosnaugh's teaching plus Miyake's general target would have led to a sequence different from presently claimed Seq ID No. 10.

Thus, the cited references provide no basis for a *prima facie* case of obviousness relative to the presently claimed invention which is directed to one specific sequence, or to a double stranded species containing this sequence as one strand as presently claimed, particularly when the art as a whole is considered, with the teaching away from start codon cites for use with RNA interference.

V. Claims 35 and 36 Are Argued Separately

Claims 35 and 35 recite the compound and the pharmaceutical composition in which the RNA is specifically identified as a double-stranded molecule of the type that is active in RNA interference techniques, with one strand being Seq ID No. 10. These RNA molecules of these claims are additionally different from the sequence of Miyake because they are double stranded. While double stranded RNA is the norm for RNA interference techniques, Miyake is a DNA

based antisense technique which functions differently.[1] The RNA sequence different from Miyake, and the Examinmer has not addressed why this change and a change to double stranded RNA would have been obvious. Thus, Applicants submit that these claims should be considered separately and are patentable on this separate ground from the other claims.

VI. Conclusion

The Examiner has failed to present a *prima facie* argument showing that the claimed invention, Seq ID No. 10, in single or double stranded form, would have been obvious over the cited references. There is merely a similar, but not identical DNA sequence, and an alternative technique. There is no connection that gets the person skilled in the art to the presently claimed sequence. Accordingly, the rejection of all claims should be reversed.

Respectfully submitted,

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[1] It is noted that during the oral argument on the decision in the parent case, the Board asked questions about apparently single-stranded RNA antisense which would hybridize with mRNA in the same manner as DNA. Such an argument would not be applicable to claims 35 and 36 of the application as now appealed.

Claims Appendix

1. An RNA molecule having a sequence effective to mediate degradation or block translation of mRNA that is the transcriptional product of a target gene, wherein the target gene encodes clusterin, and the RNA molecule comprises a sequence of bases as defined by Seq. ID No. 10.

4. The RNA molecule of claim 1, wherein the RNA molecule consists of Seq, ID No. 10.

10. A pharmaceutical composition comprising an RNA molecule having a sequence effective to mediate degradation or block translation of mRNA that is the transcriptional product of a target gene, wherein the target gene encodes clusterin, and the RNA molecule comprises a sequence of bases as defined by Seq. ID No. 10 , together with a pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10, wherein the pharmaceutically acceptable carrier is a sterile injectable solution.

14. The pharmaceutical composition of claim 10, wherein the RNA molecule consists of Seq. ID No. 10.

35. The RNA molecule of claim 1, wherein the RNA molecule is a double stranded molecule, and one of the strands consists of Seq ID No. 10.

36. The pharmaceutical composition of claim 10, wherein the RNA molecule is a double stranded molecule, and one of the strands consists of Seq ID No. 10.

Evidence Appendix

None

Related Proceedings Appendix

A Copy of the Decision in Appeal 2007-4460 is attached.

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte MARTIN GLEAVE, BURKHARD JANSEN, JOANNIS P. TROUGAKOS, EFSTATHIOS GONOS, MAXIM SIGNAEVSKY, and ELIANA BERALDI

Appeal 2007-4460
Application 10/646,436
Technology Center 1600

Decided: April 22, 2008

Before , DEMETRA J. MILLS, ERIC GRIMES, and JEFFREY N. FREDMAN *Administrative Patent Judges.*

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to RNA complementary to the human clusterin gene, which the Examiner has rejected as anticipated. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

BACKGROUND

"Clusterin is expressed in increased amounts by prostate tumor cells following androgen withdrawal. Furthermore, it has been determined that antisense therapy which reduces the expression of clusterin provides

therapeutic benefits in the treatment of cancer." (Spec. 6.) "Sequences of specific RNA molecules . . . can be used alone or in combination with other chemotherapy agents or apoptosis inducing treatment concepts in the treatment of prostate cancer, sarcomas such as osteosarcoma, renal cell carcinoma, breast cancer," etc. (*Id.*)

DISCUSSION

1. CLAIMS

Claims 1-3 and 10-13 are on appeal. Claims 4, 14, 20, 21, 23, 29, and 31-34 are also pending but are not rejected (App. Br. 1).

Claims 1-3 and 10-13 have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claims 1 and 10 are representative and reads as follows:

1. An RNA molecule having a sequence effective to mediate degradation or block translation of mRNA that is the transcriptional product of a target gene, wherein the target gene encodes clusterin, and the RNA molecule comprises a sequence of bases complementary to the gene for human clusterin.

10. A pharmaceutical composition comprising an RNA molecule having a length of less than 49 bases and having a sequence effective to mediate degradation or block translation of mRNA that is the transcriptional product of a target gene, wherein the target gene encodes clusterin, and the RNA molecule comprises a sequence of bases complementary to the gene for human clusterin, together with a pharmaceutically acceptable carrier.

2. ANTICIPATION

Claims 1-3 and 10-13 stand rejected under 35 U.S.C. § 102(e) as anticipated by Monia.[1] Claims 10 and 11 also stand rejected under 35 U.S.C. § 102(b) as anticipated by Monia.[2]

The Examiner finds that

> Monia et al. teach an oligonucleotide that can be RNA or a ribozyme (see column 6, lines 37-63) and that is targeted to clusterin mRNA (see Table 1). Monia et al. further teach the compounds are preferably from 12 to 30 nucleotides in length (see column 6, lines 54-59). Monia et al. teach a pharmaceutical composition comprising an RNA molecule and wherein the pharmaceutically acceptable carrier is a sterile injectable solution (see column 14, lines 4-10).

(Ans. 5.) The Examiner finds that Monia anticipates claims 1 and 10.

We agree. Monia teaches "antisense oligonucleotides, which are targeted to a nucleic acid encoding clusterin, and which modulate the expression of clusterin" (Monia, col. 3, ll. 33-35). Monia states that "the term 'oligonucleotide' refers to an oligomer or polymer of ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) or mimetics thereof" (*id.* at col. 6, ll. 37-40). Monia discloses numerous specific oligonucleotides that inhibit clusterin expression (*id.* at cols. 42-47). The "oligonucleotides were designed to target different regions of the human clusterin RNA" (*id.* at col.

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[1] Monia et al., U.S. Patent 6,383,808 B1, issued May 7, 2002 (application filed Sept. 11, 2000).

[2] As we understand it, the Examiner has concluded that claims 10 and 11 are not entitled to priority under 35 U.S.C. § 119(e) and therefore Monia qualifies as prior art under 35 U.S.C. § 102(b) with respect to those claims. See Office action mailed Jan. 9, 2006, page 2. The Appeal Brief and Reply Brief do not contest the denial of priority.

42, ll. 20-21). The exemplified oligonucleotides consisted of 2'-deoxy-nucleotides and 2'-methoxyethyl nucleotides, not RNA (*id.* at col. 42, ll. 31-37).

We agree with the Examiner that Monia discloses RNA molecules that inhibit clusterin expression even though it does not exemplify them. Monia discloses that antisense oligonucleotides made of either RNA or DNA inhibit clusterin expression (i.e., they either mediate degradation or block translation of the clusterin mRNA), and exemplifies inhibition of clusterin expression using numerous specific oligonucleotides.

It is true that the exemplified antisense oligonucleotides were not made of RNA. Appellants argue that this fact shows that Monia is not enabling: "Monia does [sic, does not?] provide an enabling disclosure of any species within the scope of the invention as claimed" (App. Br. 4). "[A]ll the Monia patent provides is a generic mention of RNA molecules as an alternative to the DNA species disclosed, and an invitation to experiment to find ones that may work. There is no disclosure of even one RNA sequence, and thus the reference does not place the public in possession of any embodiment within the scope of the presently claimed invention" (*id.* at 4-5).

We agree with the Examiner that Monia's disclosure is sufficient to put clusterin-inhibiting RNAs in the possession of those skilled in the art. "[A]nticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabled to one of skill in the art." *Impax Labs., Inc. v. Aventis Pharms. Inc.*, 468 F.3d 1366, 1382 (Fed. Cir. 2006) (quoting *Bristol-Myers Squibb Co. v.*

Ben Venue Labs., Inc., 246 F.3d 1368, 1378 (Fed. Cir. 2001)). And "[t]he enablement requirement for prior art to anticipate under section 102 does not require utility, unlike the enablement requirement for patents under section 112." *Id.* at 1381. Thus, the lack of actual working examples of clusterin-inhibiting RNAs does not by itself show nonenablement.

"In patent prosecution, the examiner is entitled to reject application claims as anticipated by a prior art patent without conducting an inquiry into whether or not that patent is enabled or whether or not it is the claimed material (as opposed to the unclaimed disclosures) in that patent that are at issue." *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003). "[A] presumption arises that both the claimed and unclaimed disclosures in a prior art patent are enabled." *Id.*

Monia is a prior art patent and discloses that antisense RNA molecules targeted to clusterin inhibit clusterin expression. In other words, Monia discloses that RNAs complementary to the sequence of the clusterin gene either mediate degradation or block translation of clusterin mRNA. That disclosure, which meets the limitations of instant claim 1, is entitled to a presumption of enablement. *Amgen*, 314 F.3d at 1355.

"The applicant, however, can then overcome that rejection by proving that the relevant disclosures of the prior art patent are not enabled." *Id.* In this case, Appellants have provided no evidence to show that those skilled in the art would have had to perform undue experimentation to make an RNA within the scope of claim 1 based on Monia's disclosure.

Appellants have not overcome the presumption of enablement to which Monia is entitled. We therefore affirm the rejection of claims 1-3 and

10-13 under 35 U.S.C. § 102(e) and the rejection of claims 10 and 11 under 35 U.S.C. § 102(b).

No time period for taking subsequent action in connection with this appeal may be extended under 37 CFR 1.136(a).

AFFIRMED

lp

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